Clinical Update

Naval Postgraduate Dental School
National Naval Dental Center
Bethesda, Maryland

Vol. 23, No. 2 February 2001

Recurrent Herpes Labialis (RHL)

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Purpose

Oral infection with *Herpes simplex virus* type 1 (HSV-1) is very common in the United States. Ninety percent of the adult population demonstrates antibodies to HSV-1 by the fifth decade of life (1,2). Of these, approximately 40 percent will experience a recurrent HSV-1 infection (3). The purpose of this Clinical Update is to review specifically the pathogenesis of RHL and to inform practitioners of recently published treatment options.

Pathogenesis

HSV-1 is the agent responsible for orolabial infections while HSV-2 is associated with genital infection. Both viruses can infect either location (4,5). Upon initial exposure to HSV-1, viral replication occurs at the site of infection producing primary herpetic gingivostomatitis. Upon resolution of the primary HSV infection, intact virions or viral-DNA containing capsids are transported along the periaxonal sheath of the trigeminal nerve and eventually to the trigeminal ganglion (4,5). After entering the ganglion, another round of viral replication takes place and latency is established (4). While in this latent state, the virus exists as a circular episome of viral DNA and few of its genes are expressed (3,4). Reactivation may be triggered by a variety of local and systemic stimuli such as UV light, trauma, fever, immunodeficiency, menstruation, and possibly emotional stress (3,6). The exact mechanisms involved in the latency and reactivation of HSV-1 are not yet fully understood (2,4). However, following reactivation, the virus travels down the axon to the periphery and infects the epithelial cells adjacent to the cutaneous nerve endings (7,8). The virus causes the epithelial cells to enlarge and the nuclei of the cells to degenerate. This results in the fusion of these cells to form multi-nucleated giant cells (Tzanck cells) (4). Cell lysis occurs and a clear fluid containing large quantities of the virus is released into the epidermal and dermal layers forming vesicles that rupture within 6 to 12 hours and form punctate ulcers (4,5). These ulcers may coalesce and spread to adjacent skin (5). In some cases, the host response may completely suppress lesion formation and result in asymptomatic viral shedding (5, 7). Inflammatory cells rapidly invade the ulcers of the skin and lip leading to crust formation and subsequent resolution (4). The lesions heal without scarring (3,4).

Transmission

Humans serve as the only reservoir for HSV-1 and HSV-2. No animal vectors have been identified as a means of transmission (4). Transmission of HSV-1 in susceptible individuals can occur through physical contact with vesiculo-ulcerative lesions or via individuals who may asymptomatically shed the HSV-1 virus (2,4). Abraded skin or mucosal surfaces may serve as an entry portal if contact with HSV-1 occurs (2,4). The fluid in the vesicles is teeming with the virus and is highly contagious. Patients should be cautioned against contacting the vesicles with their hands and fingers and should refrain from contacting their eyes as transmission may occur.

Clinical Features

RHL is usually preceded by a prodrome of 12 to 24 hours before vesicles appear (5). This prodrome lasts approximately 6 hours and features tingling, itching, throbbing and burning at the site of infection (5, 4). The vesicles usually appear at the skin/vermilion junction of the lip and rupture within 48 hours (4,5). Crusting of vesicles occurs within 72-96 hours of appearance and healing is usually complete within 10 days (4,5). Pain is usually most severe during the initial stages of the outbreak, and decreases over 96 - 120 hours (4). Patients with compromised immune function may have severe outbreaks of RHL that feature larger, more painful lesions of longer duration (5). Treatment with IV acyclovir and subsequent prophylaxis with oral antiviral agents may be required to prevent a fatal outcome (4).

Diagnosis

RHL is usually diagnosed by its clinical presentation but may occasionally resemble the purulent bacterial skin infection, impetigo. Should further confirmation be required, viral isolation by tissue culture is the preferred method (5,6). It may require a delay of up to 5 days and has a sensitivity rate of 70 to 80 percent. In contrast, the Tzanck smear, which attempts to identify the acantholytic Tzanck cells, will detect only about 60% of herpes infections (5). Other more sensitive tests, such as polymerase chain reaction enzyme-linked immunosorbent assay (PCR-ELISA) are very expensive and are reserved for life-threatening infections (6). Serologic tests can be used in diagnosing recurrent infections, however they may not be useful in diagnosing primary herpes due to the time required for the patient to develop circulating antibodies (6).

Treatment

There currently is no cure for RHL. Treatment goals focus on reducing the frequency of recurrent episodes, decreasing the pain and severity of outbreaks, and reducing or eliminating viral shedding (8). Treatment strategies may be classified as a) topical, b) intermittent and c) suppressive.

Topical therapy

Topical acyclovir 5% has produced studies with mixed results and has not been proven to decrease healing time. It should be reserved for immunocompromised patients only (3,6,8). Topical penciclovir (*Denavir*) is FDA approved for RHL but has been shown to decrease healing time by only one day (6,9). Recently, a topical antiviral, docosanol (*Abreva*), has gained FDA approval for over-the-counter sale (10). Studies suggest this new agent may reduce the time to healing and the severity of lesions, but comparisons to penciclovir and acyclovir have not been made (10,11).

Intermittent therapy

Intermittent therapy is instituted at the first prodromal signs or prior to exposure to an identified triggering stimulus (e.g. intense sunlight). This therapy is aimed at reducing lesion duration, pain,

and viral shedding (12). Acyclovir, valacyclovir, and famciclovir are oral antiviral agents that are FDA approved for intermittent therapy of genital herpes but not for routine use in healthy patients with RHL (12,13). Despite this, some studies and case reports have supported their benefit in some patients with RHL (4,6). A previous study suggested that administration of the bioflavonoid-ascorbic acid complex (*Peridin-C*) at the first prodromal signs may prevent the eruption of vesicles or shorten the time to healing in some patients (1).

Suppressive therapy

Current literature does not support long term treatment with antiviral drugs for the suppression of herpes labialis in immunocompetent patients (4). Oral acyclovir produces a concurrent 50% to 78% reduction in RHL in studies where patients with frequent recurrences of genital herpes (6 to 12 times per year) were prophylaxed with acyclovir (12). Additionally, some studies have associated lysine supplementation with a significant decrease in the frequency of recurrence from 4-5 lesions per year to 1-3 lesions per year (14).

Treatment Regimens

RHL is a self-limiting viral infection. In most patients, no treatment is usually required. The application of ice at the prodromal site for 30-60 minutes may reduce the severity and duration of the lesions in some patients. Those patients who suffer from frequent, severe, and debilitating recurrences may receive benefit from antiviral treatment. Treatment options are summarized below.

Preventive Treatment (15)

Rx: SPF-15 (PreSun 15) lip gel (OTC)
Disp: 15 oz
Sig: Apply to lips 1 hour before sun exposure and every hour thereafter.

Topical Treatment

Rx: Docosanol (*Abreva*) 10% cream (OTC) (10)
Disp: 1.5-g tube
Sig: Apply 5 times per day

Rx: Penciclovir 1% (*Denavir*) ointment (6)
Disp: 1.5-g tube
Sig: Apply to affected area q2h while awake

Rx: Acyclovir 5% (*Zovirax*) ointment (7,12,13)
Disp: 3 g tube
Sig: Apply to affected area q3h while awake
Reserve for immunocompromised patients.

Intermittent Treatment (12,16)

Rx: *Acyclovir: 800 mg 2x day for 5 days
or
200 mg 5x day for 5 days
or
400 mg 3x day for 5 days
*Famciclovir: 125 mg 2x day for 5 days
*Valacyclovir: 500mg 2x day for 5 days

Rx: *Peridin-C* bioflavonoid-ascorbic acid complex (OTC): 200 mg 3x day for 3 days (1)

Suppressive Nutritional Supplement (14)

Lysine: 1000 mg 1x day

*FDA approved for treatment of genital herpes. Valacyclovir is only approved for use in immunocompetent patients (12,16,17).

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